What the Cell Knows and How It Can Learn

The imprint of experience is embodied in cell structures as cultural advance is embodied in human institutions

By Salvador E. Luria

The cell is the organic substrate of all phenomena of life. In its composition and organization we must look for the basis of all vital manifestation, including learning. This restricts and yet emboldens our search; the biologist cannot fall back on any vitalistic principle, endowing matter with mind. Even a dialectical invoking of supracellular, organismic levels of complexity as the seat of the higher animal functions does not relieve us from searching the cell for the unit mechanisms underlying these functions, just as invoking the complexity of social interactions would not justify an anthropologist searching the basis of culture outside human beings. The human organism is a plurality of cells, just as human society is a plurality of men. Moreover, each man is the product of a single cell and all it knows and all it learns must be encoded or imprinted or incorporated into patterns initially provided by that cell.

What Does a Cell Know?

There are two classes of repositories of information in a cell: deterministic information and historical information. The *deterministic information* is encoded in the genes, macromolecules of nucleic acid which represent the linear tapes or templates with directions for the synthesis of enzymes and other proteins. In turn, the proteins are the machine tools and structure elements that provide and organize the machinery for the chemical tasks of the cell: compartmentalization, selective transport, and chemical transformation of substrates.

There are a few thousand genes in a bacterium, a few million in a human cell. These genes determine *what a cell can make*: whenever a gene works, a certain product will be made.

But not all this information is used all the time: in fact, most of the genetic information is not used most of the time. A highly specialized cell, for example, may use only a very small proportion of its genes, making only one or a few gene products. This is because the function of the genes is directed by another source of information, what we choose to call *historical information*. By this I mean the material imprint of all circumstances, past and present, that have been acting on a cell. Some of these are purely external, some are themselves expressions of gene function.

For example, if we remove chemically the cell wall of a bacterium, its descendants cannot start a new wall, even though they can make all the chemical pieces for a cell wall. The preexistent wall is needed to provide the framework, the informational background to assemble the pieces made under gene directions.

A third example is that of a cell that will make a certain enzyme, needed to carry out a chemical reaction, only when the proper chemical substrate is present in the medium. Here it is the external stimulus that provides the directing, historical information.

How Does a Cell Use Its Knowledge?

The key to understanding how the two sources of information—the deterministic, or genetic, or template information, and the historical, or extragenetic, or framework information—are utilized is the question of the control of gene function.

Another case in point is that of a unicellular animal called Paramecium, which has on its surface many rows of hairs or "cilia," all oriented in the same way. By an astute trick of biological surgery one can reverse the direction of the hairs in a patch of the animal's skin. From then on, in all of its descendants, the gene-produced materials that go to make hairs orient themselves in the new fashion at the spot corresponding to the patch.

The genes of a cell have the intrinsic information for making thousands or even millions of specific macromolecular products, but no cell makes more than a small fraction of them. The control mechanisms that dictate which part of the genetic information will be used and which will not are beginning to become known, at least in bacteria.

Some genes make substances called *repressors*, which prevent other genes from functioning unless a signal comes from the outside; that signal may be a chemical that inactivates the repressor or changes its specificity.

The astonishing appropriateness of cellular functions observed in bacteria—making enzymes when they are needed, reproducing various structures in precise sequence as required—is the result of the precision and effectiveness of these regulatory systems. The cell calls on genetic information as a computer calls on memory.

Does a Cell Learn, and How?

A computer "learns." Additional information is added to its memory and can be recalled by appropriate signals. Learning, according to psychologists, is "a lasting modification of stimulus-response pattern due to experience." An organism such as man can learn in this sense.

At the cellular level we have two problems: First, does a cell learn? Second, what is the cellular basis of organismic learning?

PHOTO: JEAN-PAUL REVEL, HARVARD MEDICAL SCHOOL

This electron micrograph of a mouse tumor cell shows a large nucleus (N) and nucleolus (n) and relatively little cytoplasm surrounded by the cell membrane (cm). The mitochondria (m), which are the power plant of normal cells, are poorly developed. This is a very unspecialized cell. Enlargement about 10,000 x.

Since cell functions depend on two sources of information, template information and historical information, there are two corresponding ways of changing the store of information: changes in genes and changes in their historical setting. Genetic changes, either mutations or genetic transfers, do occur in cells. This kind of learning provides the substrate for the trial-and-error process of natural selection, but it is not learning in the psychologist's sense. No one in his senses has yet made a case for gene mutation as the basis of cellular learning.

There remains another level at which cells can learn: that of their actual state, which is the result of their previous history. In terms of material cellular phenomena, we may split this area of changes into two interrelated ones: changes in gene function and changes in organization of gene products.

In a simple unicellular organism like a bacterium, we observe some elementary examples of cellular learning. For example, a bacterium may, under stimulation by a given chemical compound, start making a protein that serves to concentrate that compound inside the cells; because of this "pumping" mechanism, a high level of stimulation can then be maintained by very low external concentrations of the compound. When the compound is removed, the concentrating protein is not made any more; but the concentrating ability does not disappear completely, because the molecules of the concentrating protein are passed on intact to daughter cells generation after generation, and as long as a cell has even one such molecule it can still concentrate the compound. In other words, the learned pattern of cellular response, being embodied in a stable molecular species, is lost by dilution only. If no cell division occurred it would not be lost at all.

Learning and Differentiation

This brings us to the crux of the matter. In a complex multicellular organism specific functions become delegated to specialized cells because of stable *differentiation*. That is, once certain functions or structures of cells become manifested, they can persist because the differentiated cells do not multiply. This is true, for example, of nerve cells and muscle cells. Even if under exceptional circumstances the differentiated cells resume division, they retain some of the structures they have acquired by differentiation. In a rat, a cell that has learned to make liver enzymes may divide a few times if part of the liver is removed, but it will soon return to make liver enzymes.

WHAT is the basis of the specialized behaviors of differentiated cells? We can only guess, on the basis of models from bacteria or other microbes. A reasonable guess is the presence of feedback mechanisms involving either specific gene products or specific local patterns of organization, or both. Thus, response to a certain stimulus during differentiation may create a self-maintaining condition that increases the sensitivity of the cell to that stimulus or other specific ones.

In this sense the differentiated cell has learned.

The sensitizing condition might be the continued presence either of a stable gene product (as in the mechanism we have described above for bacteria) or of a stable pattern of gene products somewhere in the cell. In other words, as long as the cell persists, its structure and organization *are* its memory.

Such learning, it may be objected, is not learning at all: it is an increase in specialization. But this may be all there is to cellular learning during differentiation.

Cellular and Psychological Learning

What about the cellular basis of higher forms of learning? I venture to suggest that even at the level of behavioral and conceptual learning the underlying cellular mechanism will prove to be of the kind described above: persistent changes in the molecular composition and structural organization of cells. By this I do not mean the production of molecular species that are coded representations of the previous experiences. In fact, I regard with deep skepticism the repeated claims that specific learned behaviors can be transmitted from animal to animal by brain extracts.

What I mean is that the nervous system consists of cells (which are in fact the most permanent cells in the whole body) and that the response of these cells to given stimuli modifies the response of the organism to future stimuli by leaving material traces. These traces are not in the form of specific "informational molecules," but in the form of specific stable gene products—enzymes and others—whose presence and mutual interactions alter the response of the cells to future stimuli. The altered response may be the expression of changes within the nerve cells, or of changes in the pattern of contacts among nerve cells, or in the pattern of connections between nerve cells and other cells. Thus the imprint of the past experience is embodied in cell structures as a new pattern of complexity in the same way as a cultural advance is embodied in patterns of human institutions.

The analysis of the nervous system, the marvellously efficient apparatus that permits learning, memory, and concept formation, is the subject matter of neurophysiology and neuropsychology. What the cell biologist can offer today is his basic conviction that all learning of organisms must ultimately be traceable to material changes in the molecular and supramolecular oganization of cells.

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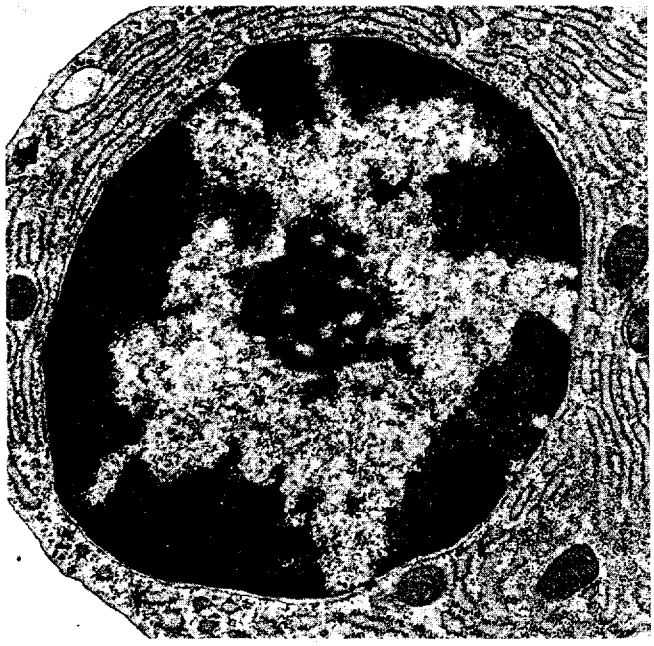

PHOTO: DON W. FAWCETT, HARVARD MEDICAL SCHOOL

This electron micrograph shows a cell specialized for production of antibodies. Comparing this cell with that pictured on the opposite page, note the vastly enlarged system of channels, along the walls of which the antibody proteins are synthesized, and the dense mitochondria, which supply the very high energy demands. Enlargement about 10,000 x.